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Review

JAK inhibition as a new treatment strategy for patients with COVID-19

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic continues to spread globally. The rapid dispersion of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 drives an urgent need for effective treatments, especially for patients who develop severe pneumonia. The excessive and uncontrolled release of pro-inflammatory cytokines has proved to be an essential factor in the rapidity of disease progression, and some cytokines are significantly associated with adverse outcomes. Most of the upregulated cytokines signal through the Janus kinase–signal transducer and activator of transcription (JAK/STAT) pathway. Therefore, blocking the exaggerated release of cytokines, including IL-2, IL-6, TNF-α, and IFNα/β/γ, by inhibiting JAK/STAT signaling will, presumably, offer favorable pharmacodynamics and present an attractive prospect. JAK inhibitors (JAKi) can also inhibit members of the numb-associated kinase (NAK) family, including AP2-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK), which regulate the angiotensin-converting enzyme 2 (ACE-2) transmembrane protein and are involved in host viral endocytosis. According to the data released from current clinical trials, JAKi treatment can effectively control the dysregulated cytokine storm and improve clinical outcomes regarding mortality, ICU admission, and discharge. There are still some concerns surrounding thromboembolic events, opportunistic infection such as *herpes zoster* virus reactivation, and repression of the host's type-I IFN-dependent immune repair for both viral and bacterial infection. However, the current JAKi clinical trials of COVID-19 raised no new safety concerns except a slightly increased risk of *herpes virus* infection. In the updated WHO guideline, Baricitinb is strongly recommended as an alternative to IL-6 receptor blockers, particularly in combination with corticosteroids, in patients with severe or critical COVID-19. Future studies will explore the application of JAKi to COVID-19 treatment in greater detail, such as the optimal timing and course of JAKi treatment, individualized medication strategies based on pharmacogenomics, and the effect of combined medications.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus underlying the coronavirus disease 2019 (COVID-19) pandemic, has posed a great challenge to public health, economic, and social stability worldwide. At the time of writing, hundreds of million people are infected, with the death toll continuously growing. Effective therapy is a vast and unmet clinical need.

Most patients with COVID-19 experience an asymptomatic or mild-to-moderate respiratory disease characterized by fever, cough, and reduced levels of lymphocytes and/or natural killer cells in peripheral blood [1]. However, approximately 5% of patients develop severe cases characterized by acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death [2-5]. Understanding the route of virus infection and the pathophysiological mechanisms of COVID-19 will help us effectively control the viral spread and prevent the disease, especially in severe cases.

There are two clinical phases of SARS-CoV-2 infection: viral infection and replication first, and the body's immune response second [6]. SARS-CoV-2 belongs to zoonotic β-coronavirus; it infects humans by binding its antigen spike protein to the human angiotensin-converting enzyme 2 (ACE-2) receptor. ACE-2 receptor is widely expressed in the type II

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[1] This paper was dedicated to Jianfeng Zhou, who unfortunately passed away not long ago.

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alveolar cells, epithelium of the mouth, tongue, and upper airways, enabling SARS-CoV-2 to enter the target cell by receptor-mediated endocytosis with the help of the cellular protease TMPRSS2 [7-12]. Epithelial type-II cells are rich with ACE-2 receptor, which explains why pulmonary infection is the most prominent clinical manifestation.

The innate immune system senses RNA viruses through toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) and then activate downstream signaling effectors such as tumor-necrotic factor (TNF)-α, interferon (IFN), interleukin (IL)-1β, IL-6 [13]. An early and robust type-I IFN response, which activates the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, is critical for protecting against viral replication and spread by initiating transcription of hundreds of IFN-stimulated genes, including pro-inflammatory cytokines [13-15].

A practical and well-coordinated immune response is the host's core defense against viral infection. While an excessive inflammatory innate response coupled with a dysregulated adaptive response may cause severe tissue damage both at the site of virus entry and at the systemic level [16]. Accumulating evidence suggested that dysregulated immune cells and molecular messengers released by them play a critical role in the pathophysiology of ARDS and MOF caused by SARS-CoV-2 infection [1,5,17-19]. Clinically, TNF-α, IFN-γ, IL-1β, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-X-C motif) ligand 10 (CXCL10), and CCL3 were elevated in the plasma of patients, which could activate and attract macrophages, monocytes, and neutrophils to inflammatory sites, resembling over-activation of innate immunity [1,17]. IL-17, GM-CSF, IL-2, IL-4, and IL-12 expressed by T helper 1 (Th1), Th2, Th9, and Th17 cells would enhance the pro-inflammatory action of autoimmune responses [1,20-22]. Among the cytokines implicated in COVID-19 associated cytokine storm, IL-2, IL-6, IL-7, IL-10, IFN-γ, G-CSF, TNF-α, and GM-CSF transmit signals predominantly via JAK/STAT pathway. Some of these, such as IL-6 and TNF-α, were directly correlated with the severity of ARDS [23-25]. This hyper-inflammatory state produces oxidative stress that damages alveolar and endothelial cells in the lungs and facilitates the progression of MOF [5,26]. Alleviating or diminishing the upregulated inflammatory response could provide a therapeutic advantage to COVID-19 patients and further improve clinical outcomes.

Therapeutic strategies that target the activated inflammatory response include cytokine monoclonal antibodies, inhibiting immune cell activation, and blocking cytokine-mediated inflammatory signal transduction [27-29]. JAK/STAT pathways transmit intracellular signals from the cell surface and participate in the cytokine-mediated immune overreaction, which eventually causes an excessive immune-inflammatory response [30]. In this review, we have recapitulated the clinical efficacy and safety of JAK inhibitors (JAKi) in the treatment of COVID-19 and highlighted the clinical value and research prospect of such therapy.

2. JAK families

Cytokine defines an extensive range of soluble molecules that ensure effective intercellular communication for developmental and homeostatic immune processes, including host defense, inflammation, trauma, and cancer [31]. These extracellular molecules can signal to the nucleus by reaching membrane receptors and/or enzymes that can phosphorylate the intracellular portion (ICP) of membrane receptors, known as the janus kinases (JAKs) [32]. Membrane receptors can be divided into two classes based on whether they have intrinsic tyrosine kinase activity [33,34]. Type I/II cytokine receptor superfamily does not possess enzymatic activities but relies on specific JAKs to transmit the signal inside the cell [30,35-37].

2.1. Members and structure of the JAK family

The human JAK family is comprised of four proteins, Jak1, Jak2, Jak3, and Tyk2, ranging in size from 120 to 140 kDa and consisting of seven conserved JAK homology (JH) domains [38,39]. Jak1, Jak2, and Tyk2 are ubiquitously expressed, while Jak3 expression is restricted mainly to immune cells [40-42]. The JAK family proteins share four domains: the kinase domain (JH1), the pseudokinase domain (JH2), the SH2-like domain (JH3-JH5), and FERM (band-four-point-one ezrin radixin moesin) domain (JH6-JH7) [43-45] (Fig. 1). The kinase domain presents catalytic activity. Recent studies have suggested that the pseudokinase domain might have an essential regulatory function, which is required to auto-inhibit the JAK kinase [46-48]. The FERM domain plays essential roles in mediating interaction with the cytokine receptor subunits and regulating catalytic activity of the C-terminal kinase domain, while the SH2-like domain can facilitate associations with the cytokine receptors through providing scaffolding [49-51]. The common mechanism of action of current JAKi is to recognize and bind to the adenosine triphosphate (ATP) binding site of the JH1 kinase domain in their active conformation [52,53].

2.2. JAK signaling pathway

When a type I/II cytokine receptor becomes bound by ligands, the active JAKs, working in pairs comprising either homodimeric or heterodimeric complexes, phosphorylate the tyrosines of ICP of membrane receptor and then the dock site of signal transmission and activator of transcription (STATs), another mediator of intercellular signaling following JAK phosphorylation. JAKs can also influence additional intercellular signaling pathways, such as PI3K/AKT/mTOR and MAPK/ERK pathways, which are strong stimulater of cell growth, proliferation, and survival [54-56].

Seven types of STATs (STAT1 to 4, STAT5A, STAT5B, and STAT6) have been identified in mammals [57,58]. Phosphorylated STATs, forming homodimers or heterodimers, migrate to the nucleus to induce and maintain immune responses via transcriptional regulation [37] (Fig. 2). These proteins constitute a rapid membrane-to-nucleus signaling transmission (JAK/STAT axis), which is involved in cell proliferation, differentiation, apoptosis, and the physiological process of the immune system (Fig. 2) [37,44,59-61]. Different ligands (cytokine or growth factor) transduce their signals through specific sets of JAKs and STATs (Table 1) [60].

2.3. Dysregulation of JAK/STAT pathway and disease

JAK/STAT signaling dysfunction leads to immunodeficiencies in mouse models and humans. *JAK* gene targeting studies have established the critical role of JAKs in vivo. Jak1 knock-out mice exhibit a lethal perinatal phenotype; $Jak2^{-/-}$ mice exhibit a mid-gestational lethal phenotype attributed to defects in erythropoiesis and responses to cytokines such as members of the IL-2 family IL-3 and IFN-γ; Disruption of Jak3 demonstrates severe defects in lymphocyte development and activity [62-65]. Loss-of-function or gain-of-function of the JAK/STAT pathway has also been observed in many immune-mediated diseases, lymphoproliferative disorders, and hematological malignancies, which characterized by uncontrolled proliferation and activation of T cell and macrophages [44,48,60,66,67]. High levels of serum pro-inflammatory cytokines such as TNF, IL-1β, IL-6, IL-8, GM-CSF, and IFN, have been proved to be a significant influencer in severe COVID-19 patients via JAK/STAT pathway [17,68]. STAT3 is also known to mediate CD8+T cell stimulation, providing a greater immune response [69].

2.4. Therapeutic potential of JAK inhibitors

Given the pathogenic role of JAK/STAT signaling in the progression of COVID-19, a new generation of small molecule inhibitors, JAKi, have

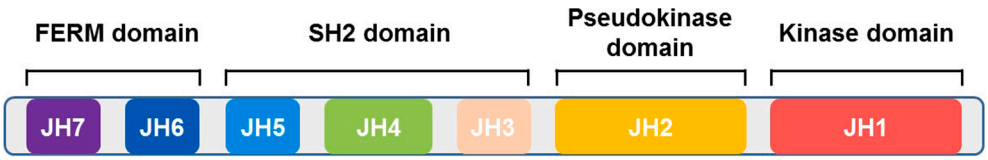

Fig. 1. Schematic of JAK structural domains. The JAK family proteins share 4 domains: the kinase domain (JH1), the pseudokinase domain (JH2), the SH2-like domain (JH3-JH5), and FERM (band-four-point-one ezrin radixin moesin) domain (JH6-JH7).

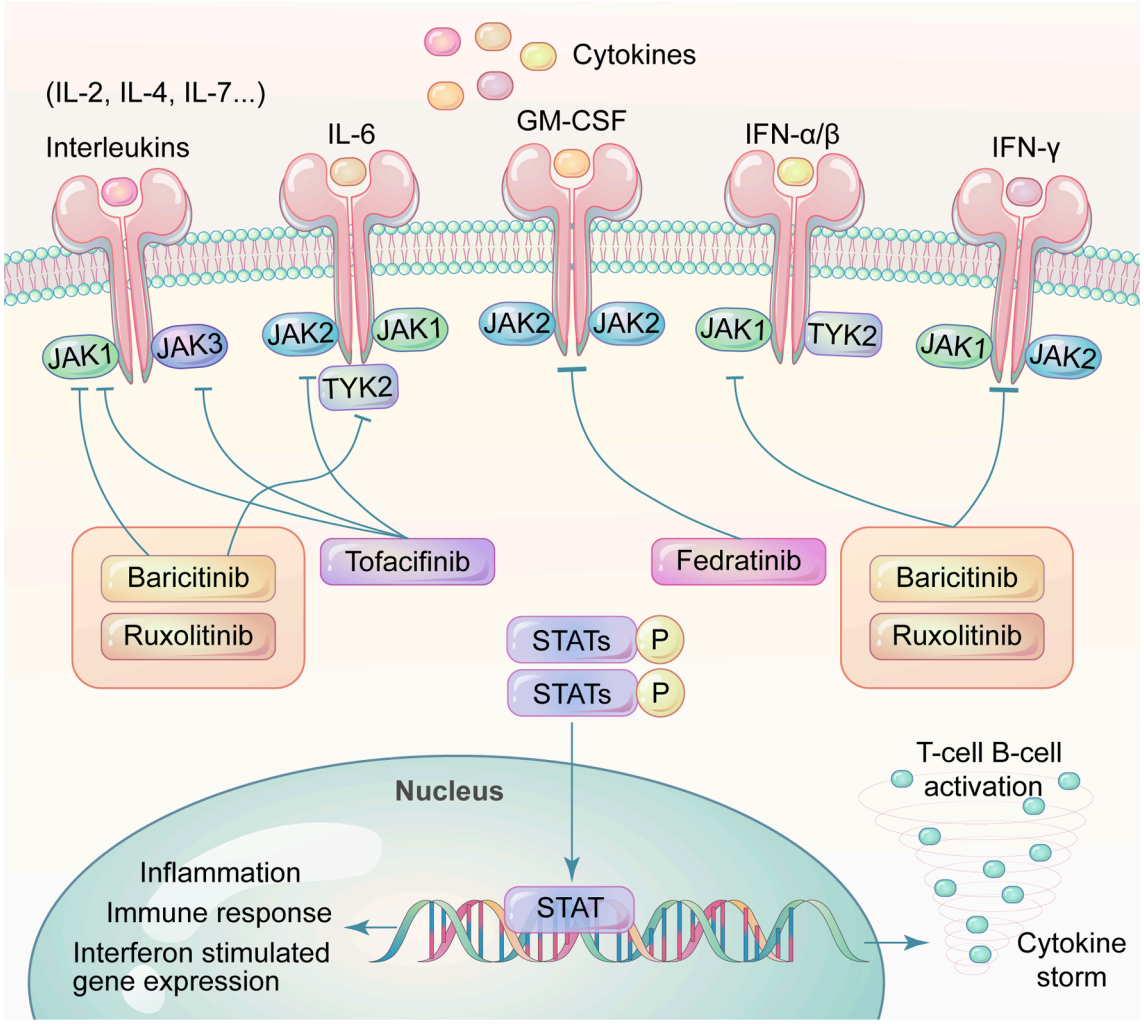

Fig. 2. Cytokine storm consequent to SARS-CoV2 infection. The human JAK family, together with the STATs, primarily contribute to signaling transmission between extracellular receptors and the cell nucleus. Excessive COVID-19 associated cytokines bind to their receptors, leading to activation of JAKs and phosphorylation of downstream STATs.downstream Phosphorylated STATs regulate interferon induced gene expression, lymphocytes differentiation and proliferation, and participate in the cytokine-mediated immune overreaction, which eventually causes an inflammatory injury at the infected organ level, even at the systemic level.

been developed to interrupt this signaling cascade in the treatment of immune-mediated disease. Baricitinib, Ruxolitinib, and Tofacitinib are the most studied inhibitors for COVID-19. They are all type I inhibitors (binding to active kinases and inhibiting them) with a relatively short half-life of 4 h for Ruxolitinib, 12.5 h for Baricitinib, and 3 h for Tofacitinib. Different JAKi inhibit different JAK isoforms, and the mechanism of action is not precisely the same [70,71].

Baricitinib was initially an oral JAK1/JAK2 inhibitor approved to treat rheumatoid arthritis (RA) [72]. Baricitinib strongly inhibits JAK1 and JAK2 enzymes (IC 50: 4.0–5.9 nM for JAK1 and 6.6–8.8 nM for JAK2), and it can also inhibit JAK3 (787 nM) and TYK2 (61 nM) in high concentrations [45,61,72,73]. Both innate and adaptive immunity can be suppressed by Baricitinib due to blocking the signaling of GM-CSF, IFN-γ, IL-8, IL-6, IL-12, and IL-23 [74-76]. Moreover, Baricitinib was independently predicted to be effective for 2019-COVID via reducing the receptor-mediated viral endocytosis by artificial intelligence algorithms at clinically achievable serum concentrations [77,78]. It has been shown to inhibit AP2-associated protein kinase-1 (AAK1) and, to a lesser degree, cyclin G-associated kinase (GAK), which may regulate the internal transport-related cell surface protein ACE-2 [79]. Its high affinity for AAK1 has been demonstrated uniquely among different JAKi in vitro assays[80-82]. In addition, recent studies have revealed that type I IFN and, to a lesser extent, type II IFN can upregulate ACE-2 expression. Baricitinib can efficiently prevent the IFN mediated increase in the expression of ACE-2, which may be beneficial in the early course of the COVID-19 [6,83].

Table 1
Summary of JAKs and corresponding STATs as well as cytokines.

JAKs	Associated STATs	Associated cytokines
JAK2	STAT1, STAT3, STAT5	IL-5, GH
JAK2	STAT3	Leptin
JAK2	STAT5	GM-CSF, EPO, PRL, TPO
JAK1, JAK2	STAT1	IFN-γ
JAK1, JAK2	STAT3	G-CSF
JAK1, JAK2	STAT1, STAT3	CLCF, IL-19, IL-20, IL-24/mda7
JAK1, JAK2	STAT1, STAT3, STAT5	IL-31
JAK1, JAK2	STAT1, STAT4	IL-35 (p35 + EBI3)
JAK1, JAK2	STAT1, STAT3, STAT4, STAT5, STAT6	TSLP
JAK1, JAK2	STAT3, STAT5	IL-3
JAK1, JAK2, TYK2	STAT3	CT-1
JAK1, JAK2, TYK2	STAT1, STAT3	IL-6, IL-11, LIF, OSM, CNTF
JAK1, JAK2, TYK2	STAT3, STAT6	IL-13
JAK1, JAK2, TYK2	STAT1, STAT3, STAT4, STAT5	IL-27 (p28 + EBI3)
JAK1, JAK3	STAT3, STAT5	IL-7, IL-2, IL-9, IL-15, IL-21
JAK1, JAK3	STAT6	IL-4
JAK1, TYK2	STAT1, STAT2, STAT3, STAT5	IL-20, IL-22, IL-28a, IL-28b, IL29
JAK1, TYK2	STAT1, STAT3	IL-10, IL-26/AK155
JAK1, TYK2	STAT1, STAT3, STAT5	IL-22/IL-TIF
JAK1, TYK2	STAT1, STAT2, STAT3, STAT4, STAT5, STAT6	IFN-α, IFN-β
TYK2, JAK2	STAT4	IL-12 (p35 + p40)
TYK2, JAK2	STAT1, STAT3, STAT4	IL-23 (p19 + p40)

GH = growth hormone; GM-CSF = granulocyte–macrophage colony stimulating factor; EPO = erythropoietin; PRL = prolactin; TPO = thrombopoietin; IFN = interferon; G-CSF = granulocyte colony stimulating factor; IL = interleukin; CT-1 = cardiotrophin-1; CLCF1 = recombinant cardiotrophin like cytokine factor 1; TSLP = recombinant human thymic stromal lymphopoietin; OSM = ontostatin M; CNTF = ciliary neurotrophic factor.

In 2011, Ruxolitinib was approved for myeloproliferative neoplasms (MPN) and steroid-refractory acute graft-versus-host disease [84,85]. Ruxolitinib has consistently demonstrated robust selective inhibition of JAK1 (3.3–6.4 nM) and JAK2 (2.8–8.8 nM) using enzymes and cell-based assays in vitro and *in vivo* [86]. The broad anti-inflammatory effects of Ruxolitinib were also observed in preclinical models and clinical studies. The immunomodulatory effect was reflected as suppressing IL-6, TNF-α, IL-12, IFN-γ, IL-18, macrophage inflammatory protein (MIP)-1α, CXCL-10, and phosphorylated STAT3, without affecting the peripheral proportion of CD4/CD8+ cells [87-90]. Its ability to activate regulatory T lymphocyte can be considered as another mechanism for its immunosuppress activity [91]. The pharmacokinetic profile of Ruxolitinib is characterized by rapid oral absorption, a short terminal elimination half-life, and a concentration-dependent and reversible pharmacodynamic effect, which ensures flexibility and effectiveness in short-term therapy [92,93].

Tofacitinib which inhibits JAK1, JAK2, and JAK3, is the first pan-JAKi to enter clinical trials for renal transplantation [94]. It inhibits mainly JAK1 (15 nM), JAK3 (45–55 nM), and to a lesser range the JAK2 (71–77 nM) and TYK2 (472–489 nM). It is a specifically potent JAK3 inhibitor, so its anti-inflammatory properties are due to its capacity to make JAKs irresponsive to multiple cytokines such as IL-2, IL-4, IL-6, IL-7, and IL-21 [91,95]. Theoretically, it may be more beneficial as it would not interact with the activation of IFNγ-mediated antibacterial immunity [96].

Overall, the SARS-CoV-2 infection triggers inflammation via the JAK/STAT signaling pathway, resulting in high levels of circulating chemokines, lymphocyte exhaustion, and uncontrolled cytokine storm especially in severe cases [13]. By blocking JAK/STAT signaling and subsequent production of cytokines, JAKi are expected to be a promising treatment for SARS-CoV-2 infection [97,98]. Several clinical trials are investigating the effects of JAKi in the treatment of COVID-19, some of which have been completed with encouraging results.

3. Performance of JAK inhibitors in clinical trials

So far, there is no specific anti-viral treatment available for COVID-19. To target the pathogenesis of SARS-CoV-2 and the role of cytokine storm in the progression of COVID-19 in severe cases, several anti-cytokine biologic therapies such as IL6 receptor antagonist, IL-1 receptor antagonist, TNF-α blocker, and JAK/STAT inhibitor, have been investigated in moderate-to-severe cases [99-102]. We will summarize the relevant discoveries of the current registered clinical trials of JAKi, which may be an effective treatment option for COVID-19.

Forty-one studies listed under clinicaltrials.gov or chiCTR.org have been included; withdrawn studies have been excluded. The drugs tested include Baricitinib (N = 16), Ruxolitinib (N = 18), Tofacitinib (N = 4), and others (N = 3).

3.1. Baricitinib

Baricitinib is an oral selective JAK1/JAK2 inhibitor licensed to treat rheumatoid arthritis (RA) that may block viral entry into pneumocytes, prevent cytokine storm, and restrain immune dysregulation in patients with SARS-CoV-2 pneumonia [83,103-105]. A total of 16 registered studies evaluated the therapeutic effects of Baricitinib (Table 2) on COVID-19 pneumonia.

The clinical benefit of Baricitinib in treating pneumonia induced by SARS-CoV-2 was first validated by a pilot study on 12 patients with moderate COVID-19 pneumonia, in which clinical and respiratory parameters significantly improved when Baricitinib (4 mg/d) was given for two weeks [104]. A large double-blind, randomized, placebo-controlled trial (NCT04401579, ACTT-2) enrolled 1,033 patients and delivered the results that Baricitinib with remdesivir was superior to remdesivir alone in reducing the median time to recovery (rate ratio for recovery, 1.16; 1.01 to1.32; p = 0.03) and improving clinical status (odds ratio, 1.3; 1.0 to 1.6). The benefit was even more apparent in patients receiving high-flow oxygen or noninvasive ventilation (rate ratio for recovery, 1.51; 1.10 to 2.08). While ACTT-2 did not detect pronounced differences in mortality between the group on the combination treatment and the group receiving remdesivir alone [106]. A phase 3, double-blind, randomized, placebo-controlled trial provided data related to overall survival (COV-BARRIER, NCT04421027). As demonstrated, Baricitinib plus standards of care (SOC) treatment were associated with significantly reduced mortality at 28 days (hazard ratio [HR] 0.57; 0.41–0.78]; p = 0.0018) and 60 days (HR 0.62; 0.47–0.83); p = 0.005), and the rate of adverse outcomes was similar between the two groups [107].

A combination of Baricitinib and corticosteroids showed significant improvement in pulmonary function compared with corticosteroids alone in moderate-to-severe SARS-CoV-2 pneumonia patients (improvement in oxygen saturation, 49; 22–77; p < 0.001) [108]. This conclusion was further confirmed by a randomized, controlled, open-label, platform trial RECOVERY study, which also demonstrated that a combination of Baricitinib with steroids had a 13% reduction in 28-day mortality for the treatment of COVID-19 (age-adjusted rate ratio 0.87; 0.77–0.98; p = 0.026, NCT04381936, RECOVERY) [109]. Another study demonstrated that an additional, single 8-mg oral loading dose of Baricitinib presented better clinical outcomes in patients with COVID-19 pneumonia, who need for intensive care and mechanical ventilation support [110].

Ongoing randomized, parallel, open-label trials (NCT04390464, TACTIC-R) will provide more information about Baricitinib in reducing the progression of COVID-19-related disease to organ failure or death compared with SOC alone [111].

Table 2
Clinical trials investigating Baricitinib in treatment of COVID-19.

Clinical trial identifier	Status	Study design	No of enrolled	Age (y)	Treatment	Outcomes
NCT04401579	Completed	double-blind, randomized, placebo-controlled trial (ACTT-2)	1033	18–99	Baricitinib (4 mg/d) + RDV vs. Placebo + RDV	Time to recovery
NCT04390464	Recruiting	Randomized, parallel arm, open-label (TACTIC-R)	1167	18 ~	Baricitinib (4 mg/d) + SOC vs. Ravulizumab + SOC	Time to the incidence of the composite endpoint of: death, mechanical ventilation, cardiovascular organ
NCT04358614	Completed	Interventional	12	12–85	Baricitinib-4 mg/d	To assess the safety of Baricitinib combined with antiviral (lopinavir-ritonavir) in terms of serious or non-serious adverse events incidence rate.
NCT04362943	Completed	Retrospective, observational, single-center cohort study	576	70~	Baricitinib vs. Anakinra	All-cause mortality
NCT04346147	Active, not recruiting	Randomized, single-center, parallel assignment, open-label	168	18~	Hydroxychloroquine + one of: Baricitinib (4 mg/d × 7 days) or Lopinavir/ritonavir or Imatinib	Time to clinical improvement on 7-point ordinal scale
NCT04320277	Not yet recruiting	Non randomized, before-after, single-center	200	18~	Baricitinib (4 mg/d x14 days) + antiviral vs. antiviral and/or hydroxychloroquine	ICU transfer
NCT04373044	Terminated	Prospective, single-arm, two center, open label	6	18~	Baricitinib (4 mg/d × 14 days) + one of: Hydroxychloroquine or Lopinavir/ritonavir/ Remdesivir	Death or mechanical ventilation at day 14
NCT04321993	Recruiting	Non randomized, multi-center, parallel assignment, open label	800	18~	Baricitinib (2 mg/d x10 days) vs. SOC	Clinical improvement on 7-point ordinal scale at day 15
NCT04421027	Completed	Randomized, double-Blind, placebo controlled, parallel assignment, interventional (COV-BARRIER)	1585	18~	Baricitinib-4 mg/d vs. placebo	Cases needing: non-invasive ventilation, high-flow oxygen, invasive mechanical ventilation
NCT04393051	Not yet recruiting	Randomized, multicentered, open-label, parallel assignment, interventional	126	18~	Baricitinib- 4 mg or 2 mg/ d for 14 days. vs. SOC	The decrease in patients requiring invasive ventilation
NCT04399798	Not yet recruiting	Single group, assignment, open-label, interventional	13	18–74	Baricitinib-4 mg/d for 7 days	Response to treatment: absence of moderate to severe oxygenation impairment
NCT04365764	Recruiting	Cross sectional, case control, observational	400	no limit	Treatment including Baricitinib vs. patients are not given treatment.	Composite of death and mechanical ventilation.
NCT04366206	Recruiting	Prospective, cohort, observational	143	no limit	Treatment including Baricitinib vs. patients are not exposed to treatment or risk factor	Composite of death and mechanical ventilation
NCT04970719	Recruiting	Interventional, randomized, parallel, assignment	382	18~	Baricitinib vs. Dexamethasone vs. Remdesivir	Rescue treatment
NCT04640168	Active, not recruiting	Randomized, parallel assignment, interventional (ACTT-4)	1010	18–99	Baricitinib Dexamethasone Placebo Remdesivir	The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: death; hospitalized, on invasive mechanical ventilation or ECMO
NCT04381936	Recruiting	Randomized, controlled, open-label platform trial (RECOVER)	8156	no limit	Baricitinib 4 mg/d for 10 days vs. UC	28-day mortality

VDR = remdesivir; SOC = standard of care; ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.

3.2. Ruxolitinib

Ruxolitinib, an inhibitor of JAK1 and JAK2 with selectivity against tyrosine kinase TYK2, was initially approved to treat neoplastic diseases [112,113]. It also showed potential therapeutic benefits for severe immune-mediated diseases such as hemophagocytic lymphohistiocytosis and severe COVID-19 cases. Eighteen live and completed studies were registered to evaluate its efficacy (Table 3).

Rosée et al. prospectively stratified 14 patients with severe COVID-19 by the newly developed COVID-19 Inflammation Score (CIS) and

Table 3
Clinical trials investigating Ruxolitinib in treatment of COVID-19.

Clinical trial identifier	Status	Study design	No. of enrolled	Age (y)	Treatment	Outcomes
ChiCTR2000029580	Completed	Single blind, randomized, parallel assignment	35	18–75	Ruxolitinib (5 mg bid) vs. placebo	Mortality; mechanical ventilation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement; time to viral clearance
NCT04338958	Completed	Single arm, non-randomized, interventional	105	18 ~	Ruxolitinib-10 mg bid increased to 20 mg bid for 7 days	Overall response rate in reversal of hyperinflammation
NCT04334044	Completed	Single group assignment, open-label, interventional	77	18 ~	Ruxolitinib- 5 mg bid	Recovery from pneumonia
NCT04377620	Terminated	Randomized, double-blinded, placebo-controlled, multicentered, interventional	211	12~	Ruxolitinib (5 mg bid) vs. Ruxolitinib (15 mg bid) + SOC	Proportion of participants who have died due to any cause
NCT04414098	Not yet recruiting	Experimental, open-label prospective, single centered, add-on, interventional	100	18~	Ruxolitinib- 5 mg bid up to 14 days and taken orally	Evaluation of Ruxolitinib efficiency in COVID-19 treatment
NCT04366232	Terminated	Randomized, open label, parallel assignment, interventional	2	18~	Ruxolitinib (5 mg bid up to 28 days + Anakinra vs. Anakinra vs. SOC	CRP, Ferritinemia, Serum creatinine, AST/ALT, Eosinophils
NCT04362137	Completed	Randomized, double-blind, placebo-controlled, multicentered, interventional	432	12~	Ruxolitinib- 5 mg bid for 14–28 days vs. placebo	Proportion of patients who die, develop respiratory failure [require mechanical ventilation] or require ICU care
NCT04331665	Terminated	Single arm, open-label, interventional	3	12~	Ruxolitinib-10 mg bid x14days following this, 5 mg bid × 2 days and then 5 mg, qd × 1 day	The proportion of ill patients with COVID-19 pneumonia who become critically ill the number of adverse events
NCT04361903	Not yet recruiting	Cohort, retrospective, monocentric, non-profit observational	18	18~	Ruxolitinib-20 mg bid in the first 48 h.	Patients avoiding mechanically assisted ventilation in ARDS occurring in COVID-19 patients
NCT04424056	Not yet recruiting	Open-label, randomized, parallel assignment, interventional	216	18–75	Anakinra and Ruxolitinib vs. Tocilizumab and Ruxolitinib vs. SOC	The number of days without mechanical ventilation at day 28
NCT04374149	Completed	Non-randomized, sequential assignment, open-label, interventional	20	12–80	Ruxolitinib (5 mg bid x14days) + TPE vs. TPE	CRP levels at baseline and day 14, cytokine levels at baseline and day 14
NCT04359290	Completed	Single group assignment, open-label, interventional	15	18~	Ruxolitinib-10 mg bid (day1) up to 15 mg bid (day2-8)	Overall survival of COVID-19 patients
NCT04477993	Terminated	Randomized, double-blind, parallel assignment, interventional (RUXO-COVID)	5	18–95	Ruxolitinib- 5 mg bid at days 0–14 vs. Placebo	Death, ICU admission, mechanical ventilation at day 14
NCT04403243	Recruiting	Randomized, open-label, parallel assignment, interventional	70	18~	Colchicine vs. Ruxolitinib 5 mg vs. Secukinumab 150 mg/ml subcutaneous solution [COSENTYX] vs. standard therapy	Change from baseline in clinical assessment score COVID 19 (CAS COVID 19) frame: baseline
NCT04348695	Recruiting	Randomized, open-label, parallel assignment, interventional	94	18~	Ruxolitinib-5 mg bid × 7 days and 10 mg bid for up to 14 days vs SOC	Cases developing severe respiratory failure
NCT04351503	Recruiting	Retrospective, observational	10,000	no limit	Current treatments including Ruxolitinib	Identification of factors associated with infection, hospitalization, and requirement of ICU treatment
NCT04278404	Recruiting	Prospective, observational	5000	~20	Under studied drugs including Ruxolitinib	Clearance, half-life, volume of distribution, elimination rate constant, half-life
NCT04581954	Recruiting	Randomized, parallel assignment, interventional	456	18~	Ruxolitinib vs. Fostamatinib vs. SOC	All-cause mortality

SOC = standard of care; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase; ICU = intensive care unit; ARDS = acute respiratory distress syndrome; TPE = therapeutic plasma exchange.

gave Ruxolitinib as treatment (NCT04338958). In their study, 12/14 patients showed a significant reduction of CIS by more than 25% on day 7 and 11/14 patients obtained sustained clinical improvement [114]. Ruxolitinib not only potently reduced ARDS-associated inflammatory cytokine levels in plasma, but was also associated with rapid respiratory and cardiac improvement. It was reported that patients treated with Ruxolitinib (5 mg twice a day) + SOC achieved faster clinical improvement and significant CT improvement when compared with the SOC group in a multicenter randomized controlled trial (ChiCTR2000029580) [115]. Ruxolitinib was also well-tolerated and associated with improved cardiopulmonary function and clinical outcomes, probably by simultaneously turning off abnormal innate and adaptive immune responses in ARDS induced by COVID-19, even in elderly patients with high-risk factors (NCT04359290 and NCT01243944) [116,117]. Another study of Ruxolitinib for the treatment of ARDS (RESPIRE, NCT04361903) suggested that Ruxolitinib administration resulted in a clinical improvement. A higher dose (20 mg bid in the first 48 h) in the early stage would improve clinical efficacy in reducing severe respiratory distress [118]. For those patients with no need for mechanical ventilation, compassionate use of Ruxolitinib (5 mg/twice daily) showed a significant reduction of inflammation biomarkers [119]. Initiating Ruxolitinib treatment immediately after respiratory symptoms begin to deteriorate, will achieve the best treatment result [118,120]. The COVID-19 CIS obtained from clinical and laboratory markers will help to define the right time to initiate the drug [114].

A novel combination of Ruxolitinib and Eculizumab to treat ARDS induced by COVID-19 was investigated in a controlled study [121]. In this study, 17 consecutive cases of SARS-CoV-2-related ARDS treated with Ruxolitinib (10 mg/twice daily) + Eculizumabor (900 mg iv/weekly) (n = 7) or the best available therapy (BAT, n = 10), and the results showed that patients treated with the combination therapy showed significantly improved respiratory symptoms. While the peripheral blood cell count was comparable between the two groups, and secondary infection was not observed in the experiment arm. In addition, lower level of circulating D-dimer was observed in the combination group compared with the BAT group.

There are several ongoing randomized, double-blind, placebo-controlled studies to assess the efficacy and safety of Ruxolitinib at different dosages (NCT04362137, NCT04377620, etc.).

3.3. Tofacitinib and other JAK inhibitors

Tofacitinib, an orally administered selective inhibitor of JAK1 and JAK3 with functional selectivity for JAK2, is under investigation in 4 registered clinical studies (Table 4). Recently, a randomized, multicenter, double-blind, placebo-controlled study (STOP-COVID, NCT04469114) conducted in Brazil revealed the significant advantages of Tofacitinib (10 mg bid) in reducing death or respiratory failure in patients hospitalized with COVID-19 pneumonia through day 28 compared with placebo (risk ratio, 0.63; 0.41 to 0.97; p = 0.04) [122]. TD-0903 (Nezulcitinib) is a pan-JAK inhibitor. A randomized, parallel assignment study (NCT04402866) was designed to evaluate this new drug's efficacy, safety, pharmacodynamics, and pharmacokinetics (Table 4). According to the early phase report, the overall mortality at day 28 was 33% in placebo-treated patients and 5% in nezulcitinib-treated patients [123]. There is another ongoing registered randomized, parallel assignment, interventional trial (NCT04404361), in which the efficacy and safety of Pacritinib, a selective JAK2 inhibitor, are evaluated in hospitalized patients with severe COVID-19 with or without cancer (Table 4). These results are worth anticipating.

4. Safety of JAK inhibitors

The risk-benefit balance must be carefully considered when using pleiotropic immunomodulators such as JAKi. Despite the beneficial effects of JAKi in preventing viral invasion and controlling dysregulated inflammation, blocking the broad range of cytokine signals transmitted via JAK/STATs may be detrimental in some circumstances. The main concerns include delaying IFN-dependent viral clearance during acute

Table 4
Clinical trials investigating Tofacitinib and other JAKi in treatment of COVID-19.

Clinical trial identifier	Status	Study design	No. of enrolled	Age(y)	Jaki	Treatment	Outcomes
NCT04415151	Terminated	Randomized, parallel assignment, interventional	24	18–99	Tofacitinib	Tofacitinib-10 mg bid followed by 5 mg bid for 0–14 days vs. Placebo	Disease severity
NCT04469114	Completed	Randomized, multicentered, double-blind, placebo controlled, interventional	289	18~	Tofacitinib	Tofacitinib-10 mg vs. placebo	Death or respiratory failure at day 28
NCT04390061	Not yet recruiting	Randomized, multicentered, open-label, interventional	116	18–65	Tofacitinib	Tofacitinib (10 mg bid) vs. Hydroxychloroquine	Prevention of severe respiratory failure requiring mechanical ventilation
NCT04332042	Not yet recruiting	Prospective cohort study, single group assignment, open-label, interventional	50	18–65	Tofacitinib	Tofacitinib- 10 mg bid for 0–14 days.	Patients requiring the use of mechanical ventilation for PaO2/FIO2 greater than 150
ChiCTR2000030170	Completed	Interventional	16	50–100	Jacketinib	Routine standard therapy + Jacketinib	Severe novel coronavirus pneumonia group: TTCI [time window: 28 days]
NCT04404361	Terminated	Randomized, parallel assignment, interventional	200	18~	Pacritinib	Pacritinib vs. Placebo	Proportion of patients who progress to IMV and/or ECMO or death during the 28 days following randomization
NCT04402866	Completed	Randomized, parallel assignment, interventional	235	18–80	TD-0903	TD-0903 (pan-JAKi) vs. placebo	Respiratory failure free days

COVID-19 = coronavirus disease 2019; PAO2 = pressure of oxygen; FIO2 = Fraction of inspiration; TTCI = time to clinical improvement; ECMO = extracorporeal membrane oxygenation.

viral infections, increasing vulnerability to secondary opportunistic infections, and thrombotic events.

4.1. Adverse events reported in immune-mediated inflammatory diseases

Inhibiting JAK-STAT signaling has been hypothesized to block downstream signals of inflammatory factors, including IFNα/β/γ, which play an essential role in responding to bacterial infection and curbing virus activity [4,124-127]. Increased risk of malignancies is the mainly concerning disadvantage of using Baricitinib for a long time [128,129]. A significant increase in the risk of *herpes zoster* infection (relative risk 1.57; 95% CI, 1.04–2.37) was suggested in a meta-analysis comprising 66,159 patients with the immune-mediated inflammatory disease, who were exposed to JAKi long term [130]. While in registered randomized, double-blind, placebo-controlled trials, rates of infectious events are only mildly increased in JAKi-treated patients over eight to 24 weeks [131-133].

Several JAKi licensed for immune-mediated inflammatory diseases have FDA black box warnings for venous and arterial thrombotic events including ischemic stroke, pulmonary embolism, and deep venous thrombosis [134,135].However, Ruxolitinib does not carry a venous thrombotic events warning. It has even been suggested to lower the inherently raised thrombotic risk in treatment for MPN [136]. A meta-analysis including 42 Phase II and III double-blinded randomized controlled trials (RCTs) of JAKi at licensed doses, involving 6,542 JAKi patient exposure years, showed that venous thromboembolism was unlikely to be substantially increased in those on JAKi therapy compared to placebo [137].

Other adverse events such as metabolism dysfunction, serious infections, cardiovascular events, and malignancy were not increased or mildly increased [138-140].

4.2. Safety profile of JAK inhibitors in clinical trials of COVID-19

Considering the proclivity to hypercoagulation in COVID-19 patients due to excessive inflammation, platelet activation, and endothelial dysfunction, whether JAKi would further increase the risk of thrombotic events was of particular concern [134,141-144]. Based on the current COVID-19 clinical trials data, no excess of thromboembolic events emerged in patients receiving JAKi [106,137,145]. Severe infections and thrombotic events were similar or even less occurred in the JAKi treatment group. The main adverse events recorded in COVID-19 clinical trials are summarized in Table 5. Evidence from Baricitinib treatment in the RA population suggested that reducing the dose (2 mg/d) may help to reduce the risk of thrombosis [128]. Further data are anticipated from the TACTIC-R and COV-BARRIER studies.

Table 5
Summary of adverse events of JAKi from registered COVID-19 clinical trials.

Clinical trial identifier	JAKi	Subjects (case vs. control or case only)	Adverse event (case vs. control or case only)
NCT04421027	Baricitinib	n = 764 vs. n = 761	serious adverse events (15% vs.18%) serious infection (9% vs.10%) venous thromboembolic events (3% vs.3%) major adverse cardiovascular events (1% vs. 1%)
NCT04401579	Baricitinib	n = 515 vs. n = 518	serious adverse events (16% vs. 21%) new infections (5.9% vs. 11.2%)
NCT04338958	Ruxolitinib	n = 105	grade 3 liver toxicity (n = 1) anemia grade 3 (n = 2)
NCT04361903	Ruxolitinib	n = 18	no drug related adverse events were observed
NCT04359290	Ruxolitinib	n = 15	adverse event (n = 2)
ChiCTR2000029580	Ruxolitinib	n = 20 vs. n = 21	hematological adverse events (65% vs. 57.1%) serious adverse events (0 vs. 19%)

Other side effects of JAKi include anemia, leukopenia, thrombocytopenia, and hyperlipidemia [146]. Therefore, JAKi are not recommended in the following situations: absolute neutrophil count less than 1×10^9 cells/L; absolute lymphocyte counts less than 0.5×10^9 cells/L; early asymptomatic infections; individuals not requiring hospital admittance [147]. These restrictions are also particularly important in severe COVID-19 cases that usually exhibit an exhausted lymphocyte phenotype. In a randomized trial of 43 patients in Wuhan, grade I to II anemia and thrombocytopenia were more common in the Ruxolitinib group. Compared with SOC, patients receiving Ruxolitinib had experienced a significantly shorter time before lymphocyte recovered [115]. However, further research data need to clarify the actual application situation in the real world.

In summary, JAKi are considered well tolerated with no new, serious safety signaling. However, information about the long-term adverse events and drug-related tumor onset is still lacking.

5. Discussion and perspectives

The incidence rate of COVID-19 increases over time, and the emergence of mutant strains makes the treatment more difficult. More efforts are being made to develop therapeutic strategies to suppress disease progression. Drug repurposing (also known as rediscovery) is an efficient way to accelerate the identification of drugs that can cure or prevent COVID-19. Significant interests are focused on the drugs, which are able to inhibit virus life circle and counteract the effects of virus infection [27,99,100,148,149]. No specific cure therapy for COVID-19 exists yet, and JAKi are the representative drugs capable of relieving systemic inflammatory symptoms and counteracting cytokine storm effects demonstrated in COVID-19. With the advantage of anti-inflammatory and anti-viral effects, convenient oral administration, and relatively short half-lives, JAKi are star molecules with great potential for clinical application [77,82,134].

A large sum of clinical evidence has represented significant therapeutic advances of JAKi in the treatment of COVID-19 pneumonia, especially for severely ill patients. Whereas different JAKi inhibit JAK isoforms with different selectivity [52,150]. The variable selectivity of JAK inhibitors is cell-dependent, dose-dependent, time-dependent, and not absolute, which may result in variability regarding their immunosuppressive effects and toxicity profile [151]. Generally, inhibiting JAK1 would block the broadest cytokine profile compared with other JAKs. JAK2, JAK3, and TYK2 were linked to erythropoiesis and thrombopoiesis, immune homeostasis, and anti-viral responses, respectively [52]. Direct comparisons from head-to-head clinical trials of JAKi are still lacking. From recent clinical experience, Baricitinib is the most extensively tested JAKi. Solid evidence from RCTs with a large sample size has demonstrated its efficacy in reducing inflammatory response, improving overall survival outcomes [106,107,109,152]. The benefit of Baricitinib is derived from multiple mechanisms, including anti-inflammation, anti-viral, and preventing the IFN-mediated increase of ACE-2 expression. Ruxolitinib has the advantages of suitable tolerance, a short half-life. Some small non-controlled studies and meta-analyses suggested the positive effect of Ruxolitinib in improving inflammatory state and clinical symptoms [114,116,117,120]. However, robust data from RCTs on survival have not been obtained until now. The recently reported randomized, double-blind, interventional phase 3 trial (STOP-COVID, NCT04469114) demonstrated that Tofacitinib treatment significantly reduced the risk of death or respiratory failure through day 28 [120]. Further evidence needs to be accumulated due to the relatively small sample size and impact of Tofacitinib on human B-cell differentiation and antibody production [122,153]. Thus, in the newly updated WHO guideline for COVID-19, only Baricitinib is strongly recommended for

severe or critical cases, especially in combination with corticosteroids [154].

Immune dysregulation is an important component of the pathophysiology of COVID-19, and remarkable successes such as the use of steroids or anti-cytokine therapies have been achieved (Table 6). Corticosteroids are considered a double-edged sword. Initially, they were only recommended in patients with SARS-CoV-2 without an alternative indication or presence of ARDS [155-159]. However, evidence showed that a short course of corticosteroids was beneficial and safe in critically ill patients with SARS-CoV-2 [156,157,160]. The results of RECOVERY showed that the use of dexamethasone (6 mg once daily administered for 10 days) has been found to be efficacious in reducing the mortality at 28 days for those patients receiving invasive mechanical ventilation (36% reduction compared with usual care group) and receiving oxygen support without invasive mechanical ventilation (18% reduction compared with control) [161]. Similar protective effects of steroids were found in the REMAP-CAP study [162]. A living network meta-analysis included 23 randomized controlled trials showed that glucocorticoids were the only intervention with evidence to reduce mortality [163,164]. An observational study enrolled patients with moderate to severe SARS-CoV-2 pneumonia and evaluated the efficacy of Baricitinib plus corticosteroids in improving the pulmonary function. It showed that a combination of Baricitinib with corticosteroids was associated with a more significant improvement in pulmonary function compared with corticosteroids alone [108]. In this study, the D-dimer level was lower in the combination group. The recently released data from the RECOVER study confirmed the combined benefit of Baricitinb and corticosteroids in reducing mortality. In this study, 95% of patients were receiving corticosteroids, and the 28-day mortality is 12%[109]. Convincing evidence for the benefits of corticosteroids in patients with moderate to severe COVID-19 disease has been provided, while it was not recommended by WHO in non-severe COVID-19 as the treatment brought no benefits [163].

Apart from corticosteroids, anti-IL-6 therapies are another beneficial strategy available (Table 6). Tocilizumab is a monoclonal antibody acting as an IL-6 inhibitor that binds to membrane-bound and soluble IL-6 receptors. The first evidence was from a retrospective study of 21 patients in China. Tocilizumab (400 mg intravenously) was used in people with severe features of COVID-19. The results indicated that Tocilizumab caused plasma CRP to return to normal levels and improved lung function [165]. Anti-IL-6 strategies are beneficial according to the recently published large-scale RCTs (RECOVERY and REMAP-CAP) and meta-analysis, which demonstrated that Tocilizumab was beneficial in patients with severe and critical COVID-19, particularly in association with glucocorticoids [166-168]. Another randomized, double-blind, placebo-controlled trial showed that Tocilizumab was ineffective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 [99]. Sarilumab is also another inhibitor of IL-6; however, the clinical studies related to Sarilumab failed to consistently demonstrate its efficacy in clinical outcome prevention [167,169].

Table 6
Overview of approved immunomodulator treatments discussed in this paper.

Immune-based therapy	Drug	Benefits	Negative indication	Clinical trial identifier	Participants
Corticosteroids	Hydrocortisone	improvement in organ support–free days within 21 days	/	NCT02735707 (REMAP-CAP)	patient admission to an ICU (n = 384)
	Methylprednisolone	/	no significant effect on the primary outcome (composite of death, admission to the intensive care unit, or requirement for noninvasive ventilation)	GLUCOCOVID	hospitalized patients receiving oxygen without mechanical ventilation (n = 64)
	Dexamethasone	reduction in mortality at day 28 in patients on mechanical ventilation and those receiving supplementary oxygen	the mortality benefit was not found among those not receiving any respiratory support at randomization	NCT04381936 (RECOVERY)	hospitalized patient (n = 6425)
	Dexamethasone	improve the number of ventilator-free at day 28	no significant difference in all-cause mortality, ICU-free days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days	NCT04327401 (CoDEX)	patients with moderate to severe ARDS in ICUs (n = 299)
	Hydrocortisone	/	no significantly in reducing treatment failure (death or persistent respiratory support) at day 21	NCT02517489 (CAPE-COVID)	patients admitted to the ICU for COVID-19-related acute respiratory failure (n = 149)
JAK inhibitor	Baricitinib (mainly)	reduction in mortality at day 28	/	NCT04381936 (RECOVERY)	hospitalized patient (n = 8156)
	Baricitinib	reduction in mortality at day 28 and day 60	no significant reduction in the frequency of disease progression	NCT04421027 (COV-BARRIER)	hospitalized adults with COVID-19 (n = 1525)
	Baricitinib + remdesivir	reducing recovery time and accelerating improvement in clinical status (notably among those receiving high-flow oxygen or noninvasive ventilation)	no significant difference in mortality at day 28 compared with remdesivir alone	NCT04401579 (ACTT2)	hospitalized adults with COVID-19 (n = 1033)
	Tofacitinib	lower risk of death or respiratory failure through day 28.	no significant difference in death from any cause	NCT04469114 (STOP-COVID)	hospitalized patients (n = 289)
IL-6 antagonist	Tocilizumab	reduction in mortality with 28-days, reduce duration of hospitalization	no benefit was found among those not receiving invasive mechanical ventilation	NCT04381936 (RECOVERY)	severe ARDS hyperinflammatory states (N = 4116)
	Tocilizumab and Sarilumab	Improving organ support–free days, 90-day survival, time to ICU, hospital discharge, and WHO ordinal scale at day 14	/	NCT02735707 (REMAP-CAP)	patients need organ support in the ICU (n = 895)
	Tocilizumab	/	not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19	NCT04356937	SARS-CoV-2 infection, hyperinflammatory states (n = 243)

ICU = intensive care unit; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; WHO = world health organization; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Indeed, the pathogenesis of COVID-19 is highly complex. At least dozens of cytokines were found to be significantly elevated in patients. Blocking IL-6 alone may be over-simplistic to counteract the establishment of the immune/inflammatory/thrombotic vicious circle [170-172]. In addition, it is difficult to monitor the degree and duration of IL-6 blockades because of the long half-life of Mabs (2–3 weeks), which may have detrimental effects such as secondary infections [173,174].

Clinical evidence on combination treatment has also emerged. Baricitinib, in combination with remdesevir, has shown to improve survival in COVID-19 patients, as demonstrated in ACTT2 [82]. Another small preliminary study evaluated the combination of Ruxolitinib and Eculizumab (an anti-C5a complement monoclonal antibody) to treat severe COVID-19 cases [121]. The results showed that the combination group had significantly improved PaO_2 and PaO_2/FiO_2 ratio. Meanwhile, the two groups had similar adverse events, including secondary infection and thrombotic events. The safety of JAKi combined with MTX or other biologics such as Tocilizumab has been confirmed [175]; however, the efficacy is still under investigation [124,176]. Numerous clinical trials are underway to explore the appropriate timing (NCT04361903), optimum administration dosage (NCT04377620), treatment course (NCT04414098), and combination with other agents such as Anakinra and Tocilizumab (NCT04366232). It is hoped that those controlled trials will contribute to establishing an optimal drug regimen of JAKi to reduce the mortality of COVID-19.

In the future, research should also focus on more precise applications of JAKi. The first-generation JAKi are pan-inhibitors that affect a broad spectrum of signaling pathways of cytokines. More and more efforts have been made to generate newer JAKi aiming to selectively target the chosen pathway to reduce the incidence of adverse events. However, it was not clear whether selective JAKi inhibitors will work better than non-selective drugs in the treatment of COVID-19. What is less clear is which particular JAKi and which route of administration will achieve the best effects with the most negligible toxicity. Currently approved JAKi are metabolized by CYP3A4 enzymes, and technology that permits genome-wide scanning may allow individualization of these drugs, thereby improving efficacy and safety. Pharmacogenomics and pharmacodynamics on JAKi and COVID-19 pneumonia will provide more evidence to identify the most benefited population and resolve drug-drug interaction problems.

Significant milestones have been reached for the severe and critical patients, but more evidence still needs to accumulate to prevent worsening of the patients with moderate disease but at high risk of progressing, and those critically ill patients with poor response to existing treatment options.

CRediT authorship contribution statement

Jin Huang: Writing – review & editing. **Chi Zhou:** Software. **Jinniu Deng:** . **Jianfeng Zhou:** Conceptualization.

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